J Physiol 587.8 (2009) pp 1669–1676

RAPID REPORT

Tibialis anterior stretch reflex in early stance is suppressed by repetitive transcranial magnetic stimulation

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A rapid plantar flexion perturbation in the early stance phase of walking elicits a large stretch reflex in tibialis anterior (TA). In this study we use repetitive transcranial magnetic stimulation (rTMS) to test if this response is mediated through a transcortical pathway. TA stretch reflexes were elicited in the early stance phase of the step cycle during treadmill walking. Twenty minutes of 1 Hz rTMS at 115% resting motor threshold (MT_r) significantly decreased ($P < 0.05$) the magnitude of the later component of the reflex at a latency of ∼100 ms up to 25 min after the rTMS. Control experiments in which stretch reflexes were elicited during sitting showed no effect on the spinally mediated short and medium latency stretch reflexes (SLR and MLR) while the long latency stretch reflex (LLR) and the motor-evoked potential (MEP) showed a significant decrease 10 min after 115% MT_r rTMS. This study demonstrates that 1 Hz rTMS applied to the leg area of the motor cortex can suppress the long latency TA stretch reflex during sitting and in the stance phase of walking. These results are in line with the hypothesis that the later component of the TA stretch reflex in the stance phase of walking is mediated by a transcortical pathway. An alternative explanation for the observed results is that the reflex is mediated by subcortical structures that are affected by the rTMS. This study also shows that rTMS may be used to study the neural control of walking.

(Resubmitted 18 January 2009; accepted after revision 23 February 2009; first published online 23 February 2009)
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Abbreviations LLR, long latency stretch reflex; MEP, motor-evoked potential; MLR, medium latency stretch reflex; MTr, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; SLR, short latency stretch reflex; SOL, soleus muscle; TA, tibialis anterior muscle; TMS, transcranial magnetic stimulation.

Human walking requires that we adapt to different terrain and ground surface irregularities. This takes place effortlessly and subconsciously through sensory feedback mechanisms within each step (e.g af Klint *et al.* 2008) as well as through predictive feedforward control mechanisms that are updated by sensory-driven error signals (e.g. Choi & Bastian, 2007). Integration of such sensory input happens at all levels of the central nervous system, including the motor cortex. Indeed, corticospinal cells in the monkey motor cortex respond at short latency to a stretch of its target muscle (Cheney & Fetz, 1984) and corticospinal neurons in the motor cortex of the standing (Karayannidou *et al.* 2008) and walking (Marple-Horvat *et al.* 1993) cat are also modulated at short latency by afferent input. There is also good evidence to suggest that transcortical reflex pathways contribute to the late component of stretch and cutaneous reflexes in the tibialis anterior (TA) muscle in sitting subjects (Nielsen *et al.* 1997; Petersen *et al.* 1998) and in the swing phase of the step-cycle during walking (Christensen *et al.* 1999, 2001).

Because the TA is normally silent during the stance phase, it is surprising that a plantar flexion imposed in the early stance phase produces a relatively large response in TA (Christensen *et al.* 2001). The latency of this response is sufficiently long to be mediated by a transcortical pathway (Petersen *et al.* 1998), although experiments to confirm this hypothesis have been inconclusive (Christensen *et al.* 2001). In this study we investigated if the TA stretch reflex in early stance phase is decreased by reducing the excitability of the leg area of the motor cortex.

DOI: 10.1113/jphysiol.2009.169367

In the hand, corticospinal excitability is reduced with 1 Hz repetitive transcranial magnetic stimulation (rTMS) applied over the motor cortex (Chen *et al.* 1997; Muellbacher *et al.* 2000; Touge *et al.* 2001; Sommer *et al.* 2002; for review see Fitzgerald *et al.* 2006). The decrease in excitability is accompanied by a decrease in the magnitude of the transcortical stretch reflex (Tsuji & Rothwell, 2002). It is unknown if rTMS applied to the leg area of the motor cortex also reduces corticospinal excitability. Therefore, to confirm that 1 Hz rTMS suppresses leg muscle corticospinal excitability we performed an initial experiment in sitting subjects, where the long latency stretch reflex (LLR) has been shown to be mediated, at least partly, by a transcortical pathway (Petersen *et al.* 1998; van Doornik *et al.* 2004). We hypothesised that rTMS primarily affects the motor cortex, and that this would be reflected by a reduction in the TMS-evoked motor potential (i.e. motor-evoked potential, MEP) and the stretch-evoked LLR without influencing the spinally mediated short (SLR) and medium (MLR) latency stretch reflexes.

With the confirmation that rTMS decreases the LLR, we tested if the TA stretch reflex in the early stance phase of walking is similarly reduced when the corticospinal excitability is decreased by 1 Hz rTMS. Such a reduction would strengthen the hypothesis that the reflex is mediated by a transcortical pathway.

Methods

Thirty healthy volunteers (age: 20–41 years, 10 females) participated in the study. The experiments were performed in accordance with the *Declaration of Helsinki*, and approved by the local ethics committee (VN-20060027). All subjects provided verbal and written informed consent.

Electromyogram (EMG)

EMGs were recorded with surface Ag–AgCl electrodes (2 cm inter-electrode spacing) placed over the tibialis anterior (TA) and soleus (SOL) of the left leg. The signals were band-pass filtered (10–1000 Hz) and amplified ($\times$2000) using custom-built amplifiers, digitised and sampled at 4000 Hz (National Instruments, Austin, TX, USA), and stored in a computer for off-line analysis.

Transcranial magnetic stimulation (TMS)

Single pulse TMS was delivered to assess corticospinal excitability. rTMS at 1 Hz was used as an intervention to decrease the corticospinal excitability. Magnetic stimuli were delivered using a Magstim Rapid^2 stimulator (Magstim Co. Ltd, Sheffield, UK) connected to a custom-made figure-of-eight coil (serial number: 8810; Magstim) placed at the spot where a magnetic stimulus gave a maximal response in the TA. Frameless stereotaxy (Brainsight, Rogue Research Inc., Montreal, Canada) allowed precise on-line monitoring of coil position and orientation with respect to the head. Coil position was maintained within 2 mm of the target.

Resting motor threshold (MT_r) was defined as the stimulator intensity at which 5 out of 10 stimuli produced a MEP greater than 50 $\mu V_{peaktopeak}$, with the TA at rest. Only in the sitting protocol, MEPs were measured at rest using intensities of 100% and 110% MT_r and during a contraction of 10 N m using an intensity of 100% MT_r. Ten trials were recorded for each condition.

The rTMS intervention consisted of 1200 pulses at 1 Hz, corresponding to 20 min of stimulation. Because it is unknown how the reduction in corticospinal excitability depends on the rTMS intensity, subjects were stimulated at 70%, 95% and 115% MT_r, with at least one week between each experiment. For the walking protocol, only 70% and 115% MT_r rTMS were used.

Stretch reflexes

Protocol 1: sitting. In this protocol it was evaluated if rTMS could suppress the (partly) cortically mediated LLR without influencing the spinally mediated SLR and MLR. Subjects were seated in a semi-reclined chair (100 deg ankle flexion; 120 deg knee flexion; 100 deg hip flexion) with the left foot strapped to a hydraulic pedal manipulandum (MTS-systems Corporation 215.35, de Zee & Voigt 2001). Visual feedback of the ankle torque was provided and the subjects were instructed to maintain a 10 N m dorsiflexion torque. The actuator delivered a 6 deg plantar flexion perturbation every 4–6 s between 80 and 140 deg s^{-1}. The speed was chosen individually for each subject so that the three distinct reflex bursts could be distinguished (see Fig. 1*B*).

Each measurement set consisted of 40 plantar flexion perturbations and three sets of 10 MEPs (one set at 100% MT_r, one set at 110% MT_r, both during rest, and one set at 100% MT_r during a contraction). To obtain a baseline, stretch reflexes and MEPs were measured twice before the intervention with at least 10 min between the measurements. The baseline was defined as the mean value from these two measures. The reflex and MEP measures were then repeated immediately after the rTMS (time zero), and 10 and 25 min after the intervention. The sequence of the protocol is illustrated in Fig. 1*A*.

Protocol 2: walking. In this protocol we tested if the TA stretch reflex in the early stance phase of walking was reduced by 1 Hz rTMS. The left leg was attached to a portable stretch device capable of delivering rapid ankle perturbations as the subject walked (Andersen & Sinkjær,

1995). Subjects walked on a treadmill at their preferred speed (range: 3.3–3.9 km h^{-1}). A force-sensitive resistor was placed under the left heel to identify heel strike. A rapid plantar flexion perturbation (6 deg, 300 deg s^{-1}) was imposed during early stance approximately 120 ms after heel contact, similar to a previous study (Christensen *et al.* 2001). The perturbations have been shown to produce a 2–4 deg knee extension compared with the unperturbed steps that occurred approximately 80 ms after the onset of perturbation, while no change in hip angle was detected (Sinkjær *et al.* 2000). If the step cycle was short, or if the response at 120 ms after heel strike was small, the perturbation was advanced by up to 45 ms. Ankle angular position was measured with an optical encoder built into the portable stretch device. Perturbations were presented pseudo-randomly every 3–5 steps.

The stretch reflex was measured in two sets before the intervention with at least 10 min rest between measurements. Each set contained at least 40 perturbed and 40 unperturbed trials. The subjects were then seated and received 1200 pulses of 1 Hz repetitive TMS. After the rTMS, the subjects started walking again and the stretch reflex was measured immediately after, 10 min after, and 25 min after the end of the rTMS.

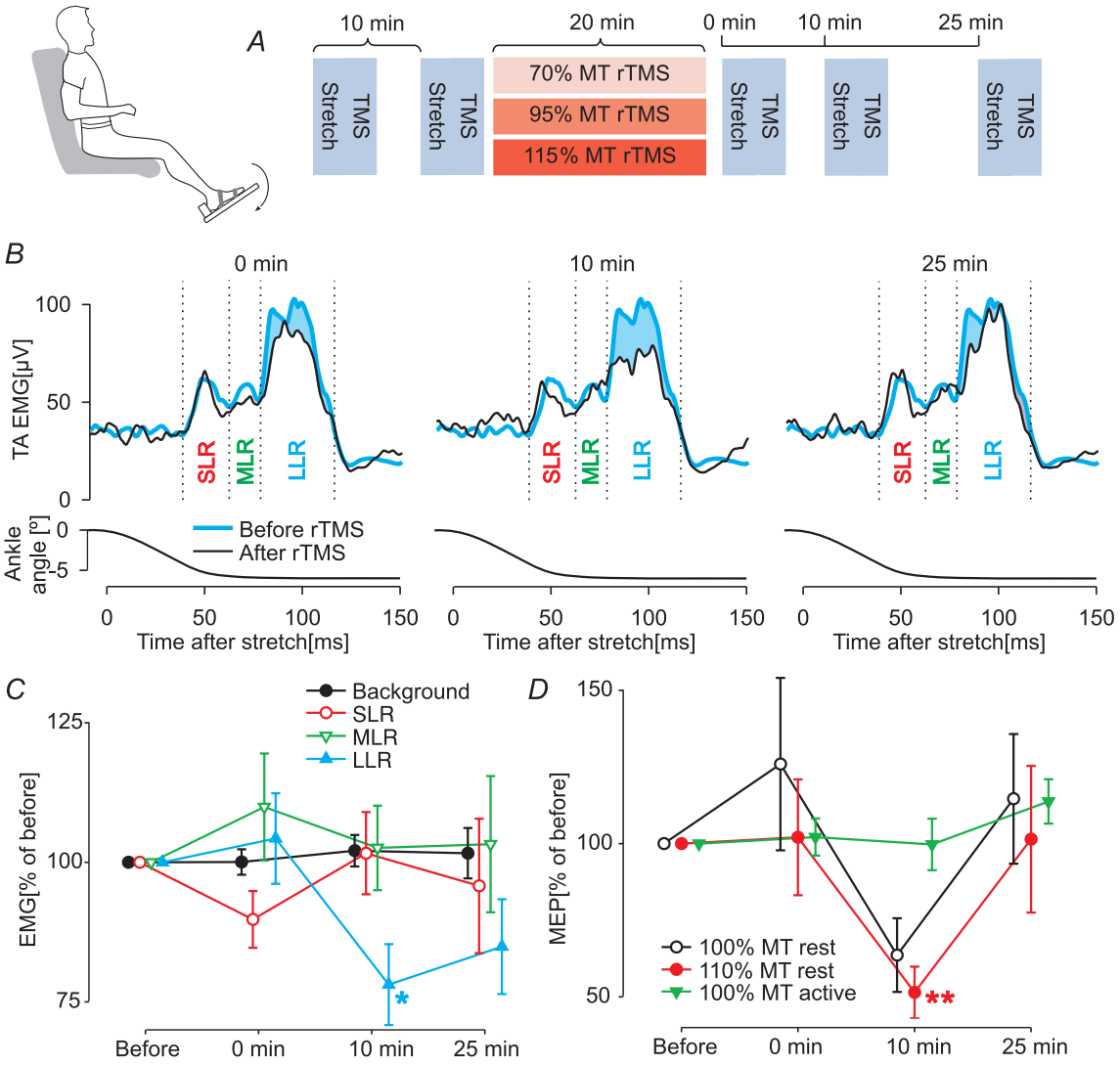

Figure 1

A, sequence of the protocol. *B*, ensemble-averaged stretch reflexes during static contraction before and after 115% MT_r rTMS for a single subject (> 40 sweeps per trace). Filled areas indicate the drop in LLR after rTMS. For display purposes the EMG data in the figures were filtered with a second-order 120 Hz zero phase low-pass filter. While this filter reduced the high frequency content of the data, no change of onsets could be observed. As an average across all subjects ($n = 11$), the effect of 115% MT_r rTMS on the stretch reflex (*C*) and MEPs (*D*) is shown. The abscissa indicates the time relative to the end of the rTMS and the values on the ordinate are a percentage relative to their value before the rTMS. $^*P < 0.05/3$, $^{**}P < 0.01/3$.

Analysis and statistics

The onset of SLR and the peaks of the different bursts were determined by visual inspection of the ensemble-averaged EMG of the responses before the rTMS. The SLR onset was defined as the first major deflection in the EMG record within a 40 ms window placed 20 ms after the onset of the perturbation. The minimum EMG level between the peak of SLR and MLR was defined as the onset of MLR and the minimum EMG level between MLR and LLR was defined as the onset of LLR. The end of LLR was defined as the time when the response returned to the baseline (see Fig. 1*B*). The mean background EMG during sitting was defined as the mean EMG in a window placed from 120 to 20 ms before the stretch. This value was subtracted from the perturbed trials. The MEPs were quantified by measuring the peak-to-peak value between 25 and 60 ms after the magnetic stimulus.

The onset of the stretch reflex in early stance was determined in the same manner as described above. Christensen *et al.* (2001) observed previously that TMS facilitated the late but not the early component of the response. Therefore, in the present study we analysed the response in two windows. Based on the window duration for the sitting protocol (SLR: 24 ± 2 ms, MLR: 27 ± 7 ms, LLR: 32 ± 8 ms), a 30 ms window was chosen for the analysis of the walking data. The first 30 ms after the onset was defined as the early component of the reflex and the consecutive 30 ms was defined as the late component of the response.

To test for differences in the intervention we used a one-way repeated measures analysis of variance (rmANOVA) with the factor time relative to intervention (before, 0, 10 and 25 min after). In the sitting protocol the effect of rTMS on SLR, MLR and LLR was tested and the threshold for significance of the rmANOVA was adjusted with a Bonferroni correction to $P < 0.05/3$. The MEP was also measured in three different conditions and therefore the threshold for significance was also taken as $P < 0.05/3$. In the walking protocol an early and a late component of the stretch reflex were tested with $P < 0.05/2$.

As a *post hoc* test, the three measurements after the rTMS were compared to the measurement before the rTMS using a paired two-sided t test with a Bonferroni adjustment. All results are presented as mean ± standard deviation. For the statistics the measured quantities were used while for the figures the averages of the comparative values are displayed as percentage change (post-rTMS/pre-rTMS) × 100.

Results

Protocol 1: sitting

Twenty subjects participated in three experimental sessions with rTMS being delivered at one of three stimulus intensities: 70% ($n = 12$), 95% ($n = 11$) and 115% MT_r ($n = 11$). Figure 1*B* illustrates representative EMG responses from a single subject before, immediately after and 10 and 25 min after applying 115% MT_r rTMS. The mean onset of the EMG responses after a stretch while sitting for all subjects was 40 ± 5 ms for SLR, 65 ± 6 ms for MLR, 90 ± 9 ms for LLR and the end of LLR was 123 ± 9 ms. No significant differences in latencies were observed before and after the intervention. The stretch reflexes from the single subject shown in Fig. 1*B* as well as the averages over all subjects in Fig. 1*C* showed a depression of the LLR response 10 min after the intervention (Fig. 1*C*; $F_{3,10} = 4.17$; $P = 0.015$; threshold $P < 0.05/3$). Also the MEP elicited with an intensity of 110% MT_r was significantly suppressed 10 min after the intervention (Fig. 1*D*; $F_{3,10} = 4.69$; $P = 0.01$; threshold $P < 0.05/3$). The MEP elicited at 100% MT_r also showed a decrease 10 min after the rTMS, but no significant differences were revealed by the rmANOVA (Fig. 1*D*; $F_{3,10} = 1.74$; $P = 0.18$). rTMS had no effect on the magnitude of the reflexes or MEPs ($P > 0.1$; threshold $P < 0.05/3$) when delivered at 70% or 95% MT_r (Fig. 2).

Protocol 2: walking

Eleven subjects participated in the walking protocol. Seven subjects participated in each of the two experimental sessions in which different stimulation intensities were used for the rTMS: 70% and 115% MT_r.

Figure 3*A* shows the EMG responses after a stretch before and after 115% MT_r rTMS. Apart from the response in TA, a suppression of the background SOL EMG was observed after the plantar flexion perturbation (Sinkjær *et al.* 2000). No changes in this decrease in SOL EMG activity were observed after the intervention. Similarly, no changes in the TA or SOL control EMG or the ankle goniometer were observed after the intervention.

The average onset of the perturbation across all subjects was 98 ± 21 ms after heel strike and the average onset of the stretch reflex was 74 ± 9 ms after this. The response was divided into two 30 ms components: an early component with an onset of 74 ± 9 ms and a late component with an onset of 104 ± 9 ms.

Figure 3*C* shows the average size of stretch reflex before and after the 115% MT_r rTMS for all subjects ($n = 7$). A one-way rmANOVA revealed significant differences in the late component of the response ($F_{3,6} = 4.63$; $P = 0.015$; threshold $P < 0.05/2$) but not in the early component ($F_{3,6} = 0.88$; $P = 0.47$) when comparing the size of the reflex after 115% MT_r rTMS with the ones before rTMS. At 70% MT_r no significant changes were observed in the early ($F_{3,6} = 1.69$; $P = 0.21$) or late ($F_{3,6} = 0.33$; $P = 0.88$) components of the response.

Discussion

In the present study we demonstrate that a remarkably large stretch reflex is evoked in the TA by an early stance phase plantar flexion perturbation; and that the reflex is suppressed following 20 min of 1 Hz rTMS applied to the leg area of the motor cortex. This observation is consistent with previous suggestions that the reflex is at least partly mediated by a transcortical pathway, underlining the notion that the motor cortex interacts with proprioceptive feedback in order to cope with the complex demands of walking (Christensen *et al.* 2001). The cortical origin of the rTMS effect is supported by the observation that the TA LLR produced during a contraction in sitting can be suppressed by rTMS, while the SLR and MLR are unaffected. These results also demonstrate that rTMS may be used to study the neural control of walking.

Mechanism of the effects of 1 Hz rTMS

Recordings of corticospinal volleys from electrodes in the epidural space in the spinal cord have recently shown that the later I-waves are diminished after 1 Hz rTMS over the hand area of the motor cortex thereby signifying that the effect is at least partly mediated by mechanisms within the motor cortex itself (Di Lazzaro *et al.* 2008). Although the coil was over the hand area of the motor cortex and caution must be exercised when extrapolating the results from rTMS studies involving the upper limbs to similar studies with the lower limbs, our observation of suppression of the MEP and the LLR is similar to previous observations in the upper limbs (e.g. Chen *et al.* 1997; Tsuji & Rothwell, 2002). Therefore, we suggest there is no reason to assume that the mechanisms of rTMS should be different for the lower limbs. In the present study, the rTMS depressed the LLR and the MEPs only when the stimulation intensity was above MT_r, in other words, only when descending volleys were produced by the stimulation. We therefore cannot rule out that rTMS exerted its effect by modulating subcortical networks. Possible differences in how the reflex during sitting and walking is mediated by such subcortical networks will reflect in different effects of the rTMS in sitting and walking.

However, the observation that the spinal SLR and MLR reflexes were unaffected by rTMS does not support the notion that rTMS affects spinal structures. Evidence has been provided in previous studies that the LLR in sitting subjects is at least partly mediated by a transcortical reflex pathway (Petersen *et al.* 1998; Van Doornik *et al.* 2004) and the selective decrease in the amplitude of the LLR following rTMS in the present study is consistent with this.

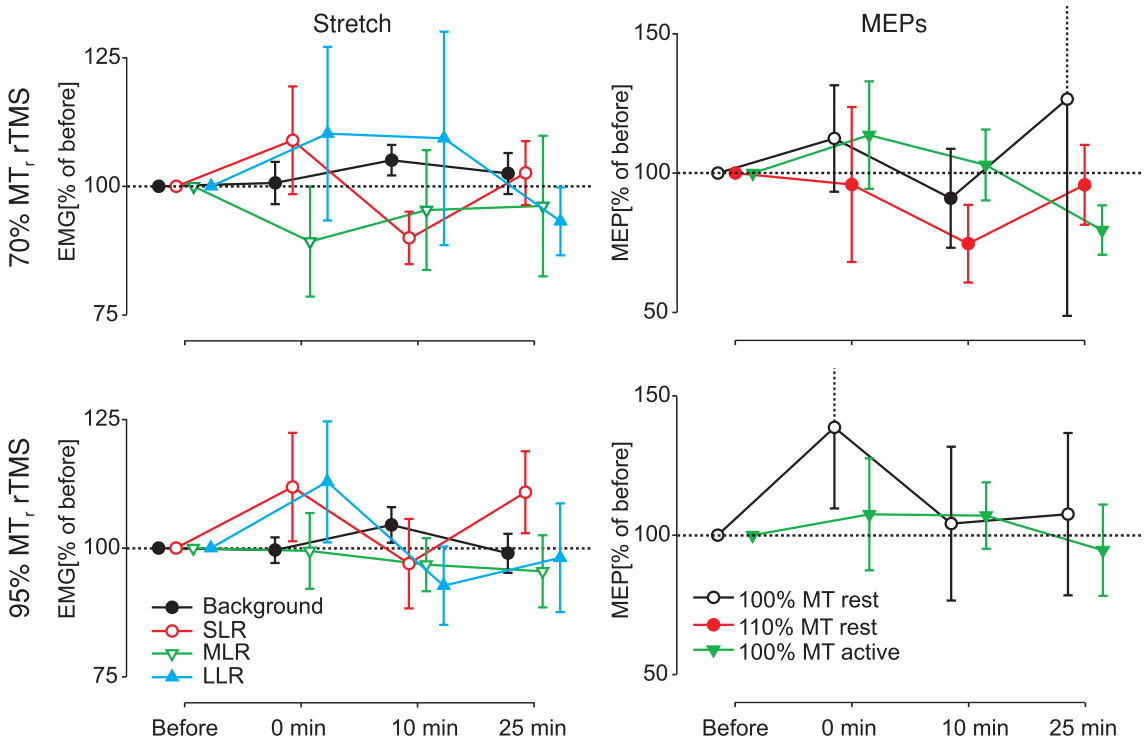

Figure 2
Effect of 70% and 95% MT_r rTMS on the stretch reflex (left) during sitting and MEPs (right). The abscissa indicates the time relative to the end of the rTMS and the values on the ordinate are relative to their value before the rTMS. No significant differences in any of the responses were observed after the rTMS.

Origin of the stretch reflex in TA in early stance

The behavioural difference between the early and late components of the reflex (Fig. 3) suggests that it is mediated by at least two separate pathways. One possible explanation is that the late part of the reflex is mediated by a transcortical pathway and suppressed by the 115% MT_r rTMS, whereas the earlier part is mediated by a subcortical pathway not affected by rTMS.

It remains uncertain as to what extent the pathways mediating the reflex observed in sitting overlap with the pathways mediating the reflex in early stance. To consistently elicit a reflex during sitting, the muscle needs to be contracted, while a reflex in early stance is readily elicited in the TA, which is slack at that time. Differences in onset latencies between the reflex in sitting and walking are also observed.

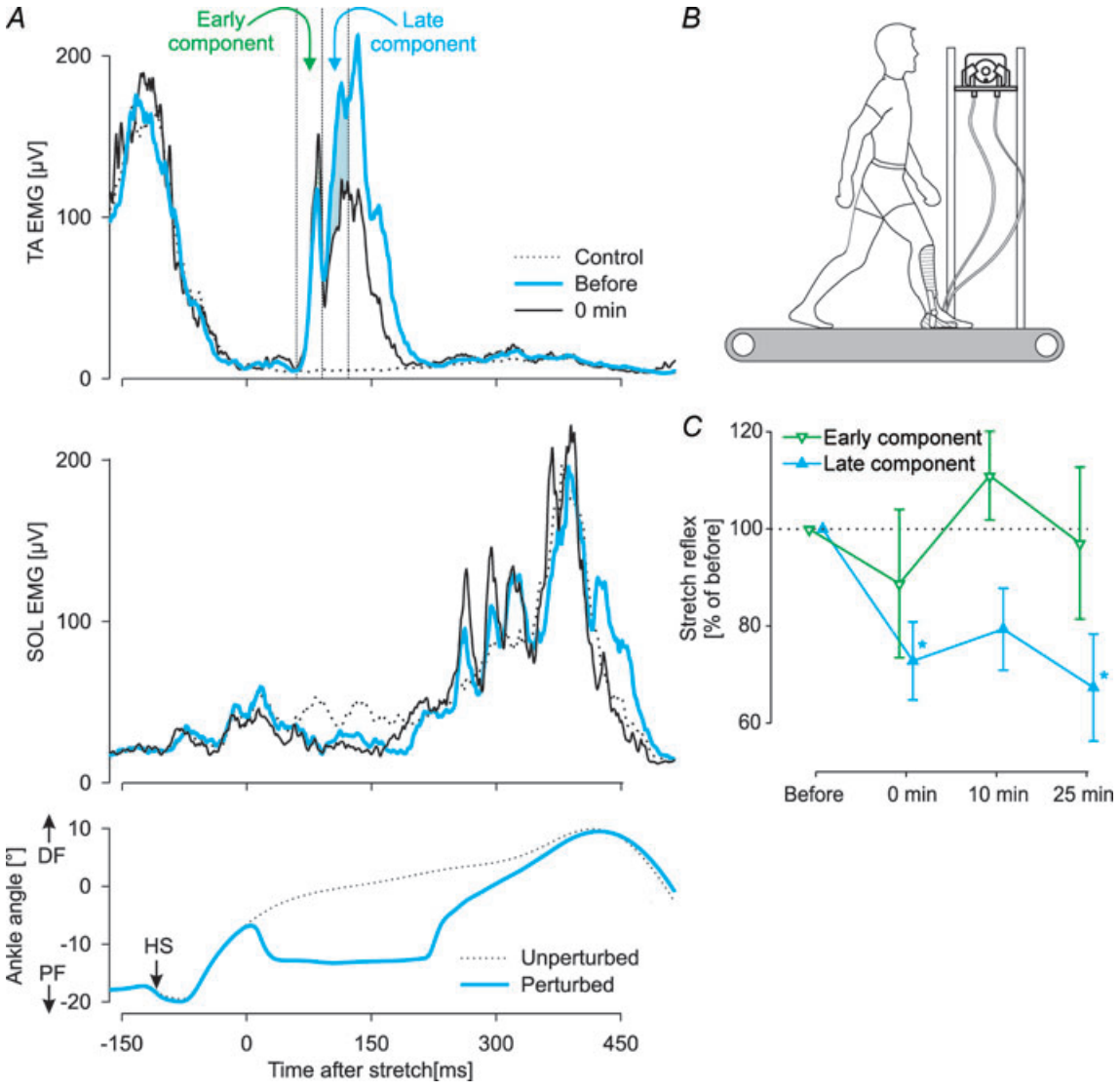

Figure 3
A, ensemble averages of the EMG responses and ankle angle after a stretch during walking from the same subject as Fig. 1. Two 30 ms analysis windows are shown (early and late components of the reflex). Note that distinct peaks are not always as clear as in this subject. It can be observed how the late component of the TA reflex is clearly suppressed following 115% MT_r, 1 Hz rTMS. The EMG data are filtered with a second-order 120 Hz zero phase low-pass filter. PF and DF indicate plantar flexion and dorsiflexion, respectively, while HS indicates heel strike. *B*, schematic diagram of the setup, showing the actuator capable of delivering a plantar flexion perturbation in early stance. *C*, average over all subjects ($n = 7$) showing how rTMS suppresses the late component of the stretch reflex and has no effect on the early component of the reflex. *$P < 0.05/3$.

During walking, the onset of the early component of the stretch response (74 ± 9 ms) is close to the MLR onset observed during a static contraction in sitting subjects (65 ± 6 ms) and it could therefore be argued that the two responses may be generated by similar pathways. Group II afferents contribute to the MLR response in TA in both standing (Corna *et al.* 1995) and walking (Grey *et al.* 2001). The small difference in MLR onset during sitting and the initial component of the stretch in the early stance phase might be explained by mechanical factors. TA is not usually active in early stance and, compared with a tonic contraction, the muscle is slack. Therefore, the difference in onset latency between walking and standing may be explained by a mechanical delay in activation of the muscle spindles.

Similarly, the onset latency of the late component of the stretch reflex during early stance (104 ± 9 ms, 30 ms window) is close to the LLR observed during a tonic contraction (90 ± 9 ms) and, again, the slack state of the TA in the stance phase of walking may explain this difference. The choice to analyse the TA stretch reflex in stance in two adjacent windows of 30 ms is based on the observation that the windows used for the analysis of the SLR, MLR and LLR during sitting are also approximately 30 ms. However, we cannot exclude the possibility that a transcortical pathway may contribute to the early component and thus contributes at latencies less than 104 ± 9 ms.

Christensen *et al*. (2001) reported a reflex onset latency of 76 ± 5 ms in 11 of 17 subjects and 92 ± 4 ms in the other 6 subjects. This bimodal distribution also supports the idea that at least two pathways mediate the stretch reflex. The onset latency of 74 ± 9 ms in the present study is comparable to the first group of Christensen *et al*. (2001), although no distinct separation between an early onset group and a late onset group was observed.

Time course of the depression

In the sitting protocol, the LLR and the MEPs were maximally suppressed 10 min after the end of the rTMS (Fig. 1*C* and *D*). In some studies the MEP depression is maximal immediately after the rTMS is delivered (Touge *et al.* 2001; Sommer *et al.* 2002). Others studies show a maximal depression after approximately 2 min (Romero *et al.* 2002), 7 min (Chen *et al.* 1997) or 10 min (Tsuji & Rothwell, 2002) following rTMS. These studies also show an effect, albeit less pronounced, immediately after rTMS rather than later in the time course. In contrast, in the present study, neither the MEP nor LLR magnitude was observed to decrease immediately after the intervention. It is possible that the rTMS intervention produces a mixture of effects, including a short lasting excitatory effect and a longer lasting suppressive effect. Different subject populations might explain the observation that a suppression of the reflex is observed immediately after the 115% MT_r rTMS during walking but not during sitting, as the effect of rTMS is known to have a high inter-individual variability (Maeda *et al.* 2000). Partly different pathways mediating the later component of the TA stretch reflex in sitting and walking cannot be excluded and a differential effect of the rTMS on each of these pathways then may explain why the reflex during walking is suppressed immediately after the rTMS while the reflex during sitting is suppressed only 10 min after the rTMS.

Epilogue

This study shows that externally elicited afferent input to the cortex can evoke descending corticospinal activity during walking. Such a transcortical stretch reflex could have the advantage of being integrated with other sensory information or motivational influences (Evarts & Tanji, 1974). The transcortical component of the response to a perturbation can therefore potentially be better adapted to the circumstances than the more stereotyped spinal reflexes.

The current study shows that interfering with the neural control of the lower limb is possible using rTMS. rTMS can be applied during sitting while its effects last long enough to be studied in a subsequent walking session. rTMS may be a valuable technique to study the neural control of walking.

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Author contributions

A. T. Zuur conducted the experiments, drafted the article, contributed to the conception and design of the experiment, analysed the data and contributed to the interpretation of the data. T. Sinkjær contributed to the conception and design of the experiment, critically reviewed the manuscript for important intellectual content and contributed to the interpretation of the data. M. S. Christensen, M. J. Grey and J. B. Nielsen contributed to the conduction of the experiments, the conception and design of the experiments, critically reviewed the manuscript for important intellectual content and contributed to the interpretation of the data. All authors gave the final approval of the version to be published.

Acknowledgements

This study was funded by the Danish Health Research Council, the Novo Nordisk Foundation, the Elsass Foundation and the Danish National Research Foundation.